

REMARKS

I. Status of the Claims

Claims 1-45 are pending in the application. Claims 1-38 have been withdrawn pursuant to a restriction requirement. Claims 39-45 have been examined and stand rejected under 35 U.S.C. §112, first paragraph. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 39-45 stand rejected under the first paragraph of §112 as lacking an enabling disclosure. The rejection appears to have two aspects. First, the examiner argues that there is insufficient evidence to demonstrate that peptides derived from MBP1, which bind to Mad2 *in vitro*, have any anti-cancer effects. Second, it is argued that "test substances" are not limited to peptides, and hence improperly encompass any number of different compounds. Applicants traverse, and will discuss each of these issues.

A. The Claims are not Drawn to Anti-Cancer Agents, but to a Screening Assay

The examiner argues that because applicants have not provided "objective evidence to show that peptides derived from MBP1 have any anti-cancer effects," nor have they "demonstrated which domain of MBP1 is involved in the interaction [with Mad2]," one of skill in the art would not know which types of peptides to screen for anti-cancer activity. Further it is argued that the art of record does not show that there are peptides that can interact with Mad2 and have anti-cancer effects.

First, applicants submit that the rejection is improper as not setting forth a proper analysis under *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Rather, the examiner has set forth a series of statements that do not address all of the issues relevant to a proper determination of enablement. As such, the rejection is improper on its face.

Second, applicants note that the claimed screening assays are two part assays. The first part merely looks for substances that bind the target polypeptide. Only the second part looks for anti-cancer activity. Thus, it is not true, as alleged by the examiner, that one of skill in the art would not know which substances should be screened for anti-cancer activity – the claim clearly states that only those substances that exhibit binding to the target polypeptide should be examined for that activity. Moreover, as stated in the specification, there is value in the assays even if no suitable candidates are identified. Specification at page 22, lines 1-4. In other words, knowing what compounds **do not** bind and/or inhibit is valuable information.

Third, it should be pointed out that the claimed screening assay is not limited to peptides (indeed, the examiner points this out in the second prong of the rejection), so the detailed discussion regarding which MBP1 peptides to screen seems misplaced. Rather, the relevance of MBP1 in the context of the claimed assays is to show that there **are**, in fact, small molecules that not only bind to Mad2 *in vitro*, but block its function. Thus, a positive control for the Mad2 binding is readily available.

Finally, what seems to be at the center of the rejection is the examiner's apparent disbelief that there is any biological significance to binding/inhibiting Mad2. This is said to derive from the lack of evidence showing anti-cancer effects of MBP1 peptides (or any other candidate substance for that matter). Applicants acknowledge that no Mad-binding has been examined for *in vivo* effects on cancer cells. However, this is not required for enablement. What

is required is that applicants' specification set forth an objective statement of enablement that the Patent Office *must* take as in compliance with §112 unless there is reason to doubt its veracity. *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971).

At pages 6-7 of the specification, the following discussion of Mad2 function is provided:

The biochemical function of Mad2 is relatively well understood. Several lines of evidence have established that Mad2 binds directly to Cdc20, a WD40 repeat-containing protein that activates APC (Li *et al.*, 1997; Fan *et al.*, 1998; Kim *et al.*, 1998; Hwang *et al.*, 1998). Thus, Mad2 prevents the activation of APC and is the most downstream component of this checkpoint pathway. Among the other known checkpoint proteins, Bub1 and BubR1 are protein kinases and both interact with Bub3, another WD-40 repeat containing protein (Taylor *et al.*, 1998). Mad1 is a coiled-coil protein and forms a tight complex with Mad2 throughout the cell cycle (Chen *et al.*, 1998; Kim *et al.*, 1998).

Experiments on mammalian cells have revealed two extraordinary features of the mitotic checkpoint. First, as a single unattached kinetochore can delay the onset of sister-chromatid separation, it must generate an inhibitory signal to block the activity of APC (Rieder *et al.*, 1995). Moreover, this signal needs to be distributed throughout the cell to account for the inhibition of APC that is not associated with the unattached kinetochore (Shah *et al.*, 2000). Second, one of the traits of the unattached kinetochores that the checkpoint senses may be the lack of tension exerted by microtubules (Li *et al.*, 1995). This notion is further strengthened by the recent finding that the kinesin-like motor, CENP-E, is an essential component of the mitotic checkpoint in mammalian cells and in *Xenopus* extracts (Abrieu *et al.*, 2000 and Yao *et al.*, 2000). CENP-E interacts directly with BubR1 in mitosis and this interaction is postulated to be a part of the force-sensing mechanism (Chan *et al.*, 1999 and Yao *et al.*, 2000).

The Mad2 protein is likely involved as the "wait anaphase" signal. First, Mad2 and Mad1 localize to unattached kinetochores (Li *et al.*, 1996; Chen *et al.*, 1998; and Chen *et al.*, 1999). When the kinetochores are captured by microtubules, the concentrations of these proteins on the kinetochores drop sharply, suggesting that they play a direct role in generating the inhibitory signals. In contrast, the kinetochore localization of Bub1, BubR1, and Bub3 persists through anaphase (Martinez-Exposito *et al.*, 1999 and Jablonski *et al.*, 1998). Second, Mad2 interacts directly with Cdc20 and inhibits the activity of APC^{Cdc20} *in vitro* (Fang *et al.*, 1998). Mad2 turns over rapidly at the unattached kinetochores (Howell *et al.*, 2000). Therefore, the unattached kinetochores may serve as catalytic sites for the generation of the active Mad2 species, which then diffuse away to inhibit APC.

In addition, Examples 1-7 provide detailed information on the nature and extent of the MBP1-Mad2 interactions. Applicants therefore affirmatively set forth evidence of enablement. No

basis has been provided to doubt this enablement and thus the holding of *In re Marzocchi* requires that the rejection under the first paragraph of §112 be removed. *Id.*

B. The Scope of Agents to be Screened is Proper

As stated above, the examiner argues that the claims are drawn to screening any agent, not just peptides. Again, there is absolutely no support given for this rejection, much less a proper *Wands* analysis. Rather, the examiner merely states that the claims cover any kind of substance, including inorganic molecules and antibodies, then concludes that “applicant has not enabled the scope of compounds encompassed by ‘substance.’” Thus, on its face, the rejection is improper.

Further, it must be emphasized here that this is a *screening* method. If applicants already knew the nature of the candidate substances that act on the target polypeptide, there would be no need to conduct the screen. The fact that one does not know what candidate substances will work highlights the need to perform screens on a wide variety of substance types. Even the ability to *exclude* classes of molecules that do *not* function as (a) binders of Mad2, and/or (b) anti-cancer agents.

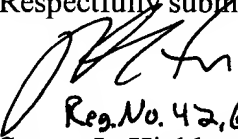
Put another way, the §112, first paragraph merely requires that one be able to make and use the claimed invention. The question then is whether the scope of potential candidate substances prevents one from running the assay and determining the result. Clearly, the answer is “no.” *Any* test substance may be used in the assay, and the fact that some (in fact most) may not bind Mad2 or inhibit cancer is irrelevant to enablement. Again, the point of the assay is to *screen*, and thus there is a presumption that not all candidate substances will be identified as having the desired properties.

In conclusion, applicants submit that the present invention provides a basic tool for examining the biological function of a wide variety of test substances. As such, the broad scope of candidate substances to be tested is indeed proper. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

III. Conclusion

Applicants respectfully submit that all claims are in condition for allowance, and an The Examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,


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